SYNTHESIS AND CHARACTERIZATION OF TRANSITION METAL COMPLEXES AND THEIR BIOLOGICAL ACTIVITY

A SYNOPSIS OF THE PROPOSED RESEARCH WORK SUBMITTED TO THE SWAMI RAMANAND TEERTH MARATHAWADA UNIVERSITY, NANDED

FOR

THE DEGREE OF DOCTER OF PHILOSOPHY

IN

CHEMISTRY

BY

Mr. AUDUMBAR DATTATRAYA CHAVAN

M.Sc.(Org. Chem.) B. Ed.

UNDER THE GUIDENCE OF

Dr. S.D. Dhage

M.Sc. M. Phil. Ph D.

(Research Guide in Chemistry)

SSJES, ARTS, COMM. AND SCIENCE COLLEGE, GANGAKHED, DIST. PARBHANI

SWAMI RAMANAND TEERTHA MARATHAWADA

UNIVERSITY, NANDED 431605

MAHARASHTRA

Synthesis & characterization of transition metal complexes & their Biological activity

Introduce transition metals in more detail.

Abstract :-

Transition metals have an important place within medicinal inorganic chemistry. Transition metals are included in d- block elements. They are bridge between S & P block. Some of these transition metals are applied today's medicinal chemistry. Pharmaceutical products are prepared from these elements. Cu, Mn, Co, Fe, V these elements are d- block elements. Zn powder is useful for maize crops increasing yield.

Still there is groom to improve the performance. Our aim to develop new metal complexes having biological activities yet to be studied.

Transition metals exhibit different oxidation states & can interact with a number of negatively charged molecules. Metal are very useful from ancient time for human beings. Metals are used as good conductor of heat & electricity, for old era they are utilized for weapons. Later on they are helpful for curing human diseases, Gold, Silver these are helpful for jwellery prepatation.

In modern world semi-conductors super conductors are prepared from metals. Nonmaterial are also useful applications of metals. Nanotechnology is an branch being tool for synthesis of nonmaterial's from nano-particles (NPCs). This activity of transition metals is used for pharmacological & therapeutic applications. In pharmacological screenings like anti- microbial, anti- inflammatory & anti-tumor action of synthetic transition metal complexes places are applied. First row transition metal complexes Mn, Co, Ni, Cu, Zn, V & traces pharmacological applications of these Co-ordination compounds. Metal ion complexes are playing an increasing role in the development of antimicrobials. Anti-microbial properties of cobalt co-ordination complexes containing polydentate donor ligands which focus on anti-microbial activity of the homoleptic $[Co(NH_3)_6]$ ion.

1) Introduction:-

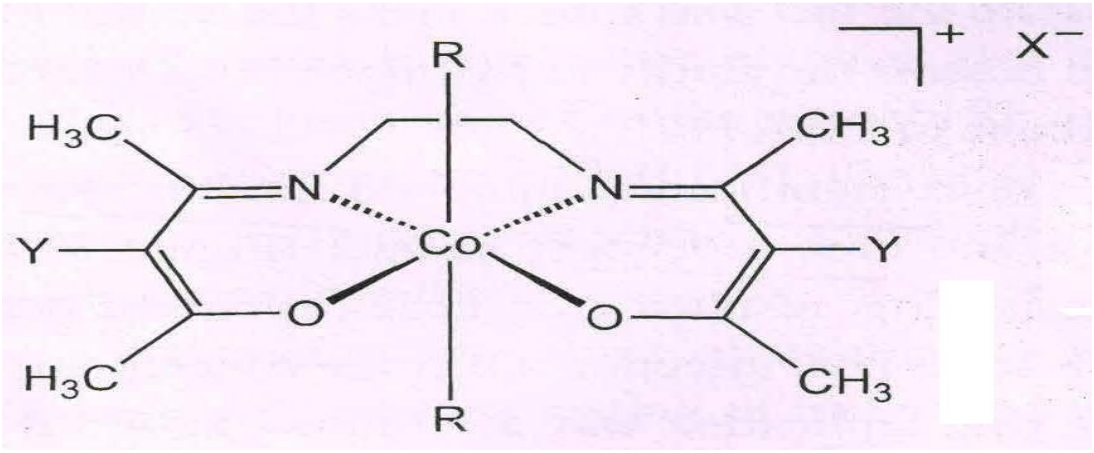
Metal ions play important roles in biological processes & it is concerned with application of inorganic chemistry to therapy or diagnosis of diseases is medical inorganic chemistry. Metals have been used in the treatment diseases of humans since ancient times. It historically proven use of metals in pharmaceutical which traces back to the ancient civilizations of Egypt, India, Mesopotamia & china. Metals ions binding components into a biological system for treatment of diseases is main field of bioinorganic chemistry.

Transition metal complexes gives advantages is DNA- binding agents. DNA foot printing agents is an application of metal complexes.

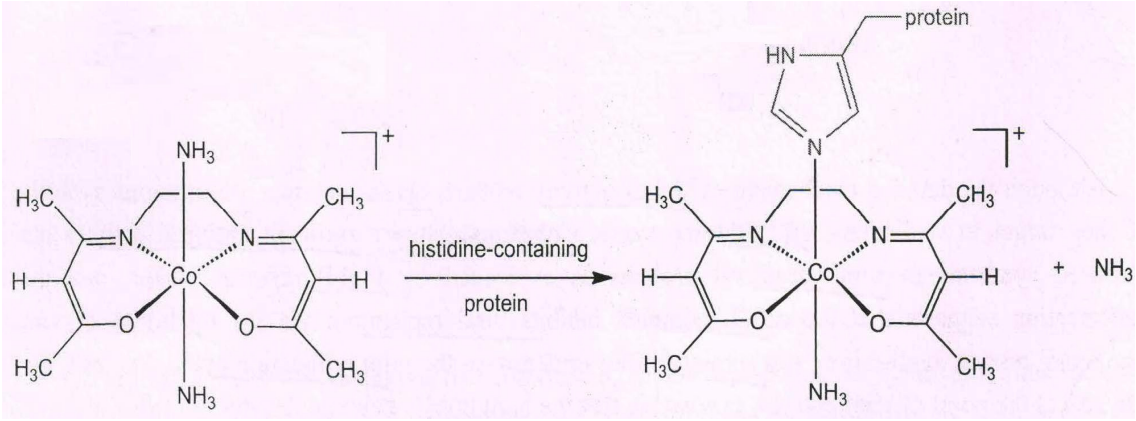
Cobalt (III) based ligand complexes have been to have both antiviral & antimicrobial activities antifungal, anticancer applications.

2) Biological Significance of metal complexes:-

Millennia which an empirical evidence for the effectiveness of metal based therapeutics, Bioinorganic chemistry, pathologists pharmacologists & oncologists which gives the relationship between metals & cancer.



Cobalt transition complexes (CTC) compounds having potential application in the treatment of human immunodeficiency virus 1 (HIV-1).



Cohex having potent antiviral activity

3) DNA – metal complex Interactions:-

Cu is found in all living organisms & it is vital trace element in redox Chemistry, growth & development. Cu is significant for enzymes & proteins involved in energy metabolism respiration & DNA Synthesis. Copper is found to bind DNA with high affinity than any other divalent cation, thus promoting DNA oxidation.

4) Pharmacological Actions:-

Chemotherapy using chemical agents is one of the best methods for the treatment of various cancer.

5) Anti-Microbial Agents:-

Following Structure shows potent antimicrobial agents.

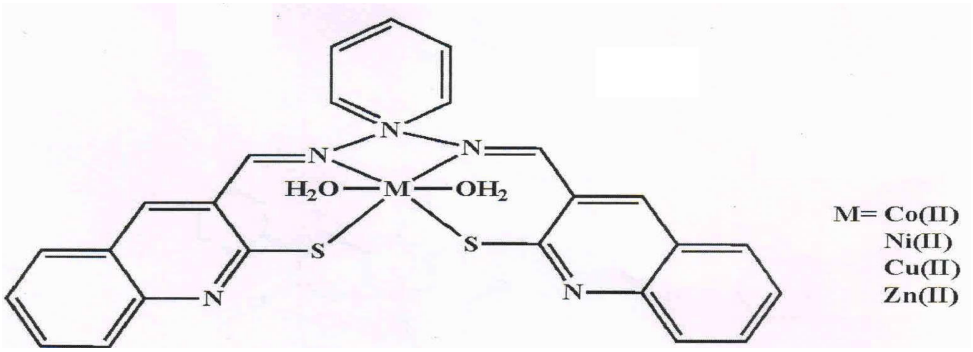
Anti- tumor agents:-

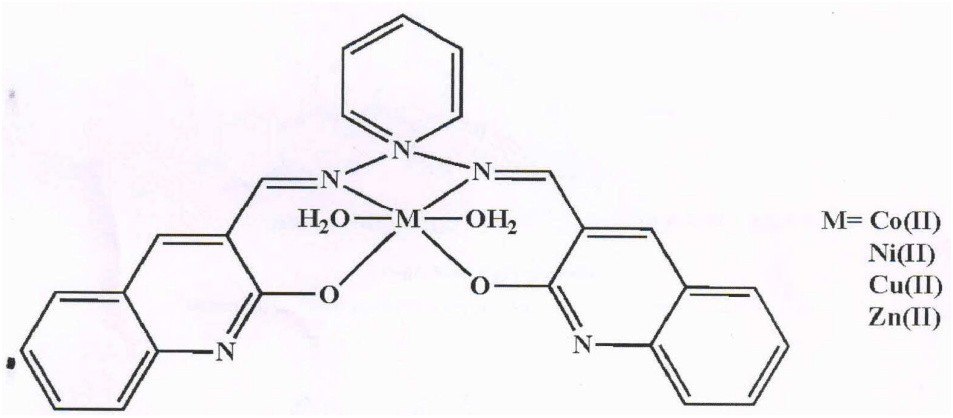
Copper (II) complexes has high nucleobase affinity & biologically redox potentials are considered as potential reagents for cleavage of DNA.

Metal Complexes would permit targeting of specific DNA sites by matching the shape, Symmetry.

Anti – inflammatory Agents:-

Chemical Structures of Cu(II), Co(II), Ni(II) & Zn(II) complexes with Schiff bases derived from 2- Mercapt 0-3 Formylquinoline is shown in following structures.





Objectives of Research / Proposed Hypothesis:-

1) To analyze & identify the structures of the synthesized metal complexes by combining different spectroscopic techniques such as IR (infrared), proton-NMR, spectroscopy.

2) To test the biological activities of metal complexes.

3) Thermal study of complexes.

4) Methodology to be adopted:-

a) STATEMENT OF HYPOTHESIS

b) METHODS OF DATA COLLECTION

c) PROBABLE METHODS OF DATA ANALXSIS

Following are the some analytical methods can be applied.

i) IR Spectroscopic Methods:-

Several IR Spectroscopic tests have been widely developed to quantity metal complexes. Infrared spectral data of metal complexes & ligands gives different frequency bands on which bonling has been studied.

ii) Biological Activities:-

a) Anti – Microbial

b) Anti – Tumor

c) Anti – Inflammatory

iii) Thermal Study of Analysis:-

Thermo gravimetric analysis (TGA) Study of metal complexes & DTA (Differential thermal analysis) techniques are can be used to determine the decomposition nature of complex.

5) Importance of Study / Society applications:-

International Status:-

i) Center for Bio science & Engineering, Naval Research Laboratory, Washington, USA, Chemistry Department, Florida Institute of Technology, 150 West University Boulevard, Melbourne had been done research on cobalt complexes as Antiviral & Anti-bacterial studies in April 2010.

ii) National Science Centre of the polish Ministry of science and Higher Education had been worked in December 2016.

iii) University of Toranto ; Canada gives brief research of biological chemistry of Nicked in 2017.

National Status :-

In India huge ammount of research has been done on metal complexes.

i) SRTM university Nanded in which synthesis & characterization of transition metal complexes of Schiff base derived from Isatin & 2- amino, 4- chlorobenzoic acid had been worked in 2012.

ii) PG & Research Department of chemistry Auxilium college, vellore, Tamil Nadu gives research article on synthesis & biological application 4- isopropyl benzaldehyde & their Mn(II), Fe(III) metal complexes in 2014.

iii) Pharmacological Activity of a few transition metal complexes work was done in 2016 by Department of chem.. Dr. MGR Educational & Research Institute University, Chennai, India.

iv) Department of Inorganic Chemistry, School of Chemistry, Madurai Kamraj University, Madurai.

India given brief research article on Synthesis, Characterization & anti- bacterial activity of divalent transition metal complexes of hydrazine & trimetric acid in Journal of Saudi Chemical Society in feb 2017.

Significance of the Study :-

Research is an path for helping to the human society. Many biological activities Studies such ant- tumor, anti-inflammatory, anti-microbial are very needful for today community.

Metal complexes are used in anti cancer drugs in pharmaceutical industry. NCL (National Chemical Lab) Pune also works on it.

Medicinal – inorganic chemistry in which transition metals have an important place.

Therapeutic applications of metal complexes it an significance of the study.

6) Proposed Work Plan / Formulation & Structure of Study:-

The Proposed work will be completed in four parts:-

Phase I:-

The first phase involves the literature survey & regarding advanced techniques, method development & analysis using proposed methods like TGA & complete the Ph.D course work in due time.

Phase II :-

Second phase covers synthesis of metal complexes & their spectroscopes likewise P-NMR IR- Spectroscopy.

Phase III:-

Development of biological activity & TGA studies of metal complexes.

Phase IV:-

The last phase consists of analysis data collection, compilation & publication of article.

7) References:-

1) J.F.M. Da Silva, S.J. Garden and A.C. Pinto, J. Braz. Chem. SOC, 67(3), 273(2001).

2) E.M. Joud, G Larcher. M. Allian A. Riou, G.M. Bow, M.A. Khan, X. Do Thanh, J. Inorg Biochem; 86, 565(2001).

3) S.N. Pandeya, D. Sriram, P. Yogeswari, S. Ananthan; Chemotherapy, 47, 266 (2201).

4) S.S. Kontstantinovic, B.C. Radovanovic, Z. V.Vasic, J. Serb. Chem.. Soc. 68, 641 (2003).

5) R.Bartha and E.J. Ordal, J. Bacteriol., 1965, 89, 1015.

6) P.Schonheit, J. Moll and R. k. Thauer, arch. Microbiol., 1979, 123, 105.

7) N. E. Dixon, C. Gazzola, R.L. Blakeley and B.Zermer, J. Am. Chem. Soc., 1975, 97, 4131.

8) J.C. Polacco, Plant Physiol., 1977, 59, 827.

9) G. B. Diekert, E.G. Graf and R. K. Thauer,Arch. Micribiol., 1979, 122, 117.

10) J. L. Boer, S. B. Mulrooney and R. P. Hausinger, Arch. Biochem. Biophys., 2014, 544, 142.

11) Y. Li and D. B. Zamble, Chem. Rev., 2009, 109, 4617.

12) M. J. Maroney, Curr. Opin. Chem. Biol., 1999, 3, 188.

13) S.W. Ragsdale,J. Biol. Chem., 2009, 284, 18571.

14) Nickel and its Surprising Impact in Nature, ed. A. Sigelk, H. Sigel and R. K. O. Sigel, John Wiley & Sons Ltd, Chichester, 2007, vol. 2.

15) M. J. Maroney and S.ciurli, Chem. Rev., 2014, 114, 4206.

16) S. W.Ragsdale, J. Inorg. Biochem., 2007, 101, 1657.

17) R. K. Thauer, A.-K. Kaster, M. Goenrich, M. Schick, T. Hiromoto and S. shima, Annu. Rev. Biochem., 2010, 79, 507.

18) M. C. Weiss, F. L. Sousa, N. Mrnjavac, S. Neukirchen, M. Roettger, S. Nelson-Sathi and W. F. Martin, Nat. Microbiol., 2016, 1, 16116.

19) S. E. McGlynn, D. W. Mulder, E. M. Shwperd, J. B. Broderick and J. W. Peters, Dalton Trans., 2009, 4274.

20) M. J. Russell and W. Martin, Trends Biochem. Sci., 2004, 29, 358.

21) Y. Sheng, I.A. Abreu, D.E. Cabelli, M.J. Maroney, A.-F. Miller, M. Teixeira and J.S. Valentine , Chem. Rev., 2014, 114, 3854.

22) S.Pizzutelli, Eur. Ann. Allergy Clin. Immunol., 2011, 43, 5.

23) IARC, IARC Monogr. Eval. Carcinog. Risks Hum., 2012, 100C, 169.

24) F. H. Nielsen, in Present Knowledge in nutrition, ed. J. W. Erdman jr, I. A. Macdonald and S. H. Zeisel, Wiley-Blackwell, 10 edn, 2012, p. 586.

25) T. Phipps, S.L. Tank, J. Wirtz, L. Brewer, A. Coyner , L.S. Ortego and A. Fairbrother, Environ. Rev., 2002, 10, 209.

26) S. Nomoto, M. D. McNeely and F. W. Sunderman Jr, Biochemistry, 1971, 10, 1647.

27) J. P. Thyssen, D.J. Gawkrodger, I. R. White, A.Julander, T.Menne and C. Liden, Contact Dermatitis, 2012, 68, 3.

28) F. O. Nestle, H. Speidel and M.O. Speidel, Nature, 2002, 419, 132.

29) M. Schmidt and M. Goebeler, J. Mol. Med., 2011, 89, 961.

30) R. Spiewak, J.Pietowska and K. Curzytek, Expert Rev. Clin. Immunol., 2007, 3, 851.

31) M. Schmidt, B. Raghavan, V. Muller, T. Vogl, G. Fejer, S. Tchaptchet, S. Keck, C. Kalis, P.J. Nielsen, C. Galanos, J. Roth, A. Skerra, S.F. Martin, M. A. Freudenberg and M. Goebeler, Nat. Immunol., 2010, 11, 814

32) E. Schwartz, J. Fritsch and B. Friedrich, in The Prokaryotes-Prokaryotic Physiology and Biochemistry, ed. E. Rosenberg, Springer-Verlag, Berling, 2013, p. 119

33) P.M. Vignais and B. Billoud, Chem. Rev., 2007, 107, 4206

34) M.Can, F.A. Armstrong and S.W. Ragsdale, Chem. Rev., 2014, 114, 4149

35) Y. Zhang and V.N. Gladyshev, J. Biol. Chem., 2010, 285, 3393

36) P.T. Chivers, Metallomics, 2015, 7, 590

37) B. Desguin, T. Zhang, P. Soumillion, P. Hols, J. Hu and R. P. Hausinger, Science, 2015, 349, 66

38) J.FM. Da Silva, S.J. Garden and A.C. Pinto, J. Braze. Chem. Soc., 67 (3), 273(2001)

39) E.M. Jouad, G. Larcher. M. Allian. A. Riou, G.M. Bouet, M.A. Khan, X. Do Thanh, J. Inorg. Biochem., 86 565(2001)

40) S.N. Pandeya, D.Sriram, P. Yogeeswari, S. Ananthan; Chemotherapy, 47, 266(2001)

41) S.N. Paneya, D. Sriram, G. Nath, E. De Clercq, Arzein-Forsch/Drug Res., 50, 55(2000)

42) S.S. Konstantinovic, B.C. Radovanovic, Z. Cakic, V. Vasic, J. Serb. Chem. Soc., 68, 641(2003)

43) G. Fachinetti, C. Floriani and P. Zannazzi, Inorg. Chem., 18, 3469(1979)

44) M.D. Hobday, T.D. Smith, J. Chem. Soc. Datton Trans., 20, 2287(1972)

45) X. Shin, Q.LC Yang, Y. Xie, Synth. React. Inorg. Met. Org. Chem., 26, 1135(1996)

46) P.R. Reddy and A.M. Reddy, IJC, 41A, 2083(2002)

47) B.Thirumagal, S. Malik and A. Balasubramaniam, The Pharmacist, 3(1), 27(2008)

48) N. Sari, P. Gurkan, S. Cete and I. Sakiyan, Russian J. of Coordination Chem., 32(7), 511(2006)

49) Angela Kriza, Carmen Parnau, N. Popu and T. Rosu, Analele Universitatii din Bucuresti Chimi, Anul XIII (Serie noua) I-II, 179(2004)

50) E. Conpolat and M. Kaya, Transition Metal Chemistry, 29, 550(2004)

51) M.M. El-ajaily, F.I. El-Moshaty, R.S. El-zweay and A.M. Maihub, I.J. of Chem. Tech. Research, 1(1), 80(2009)

52) B. Kumar, K.K. Prasad and S.K. Srivastawa, Oriental Journal of Chemistry, 26(4), 1413(2010)

53) S. Malik, S. Ghosh and B. Jain. Arch, Apll, Sci. Res., 2(2), 304(2010)

54) B.H.M. Maruthyunjaya Swamy, O.M. Ijare and Y. Jadegoud, J. Braz. Chem. Soc. 16(4), 783(2005)

55) K. Rathore, R.R. Singh and H.B. Singh, E-Journal of chemistry, 7(S1), S 556(2010)

56) M.B. Halli, Z.S. Qureshi, P. Vittal, B.N. Jumanal and V.B. Patil, J. Ind. Council Chem. 25(1), 1(2008)

57) S.R. Pingalkar and M.N. Deshpande, Orient J. Chem., 23(1), 265(2007)

58) N.S. Youssefl and K.H. Hegab, J. Mater. Sci. Technol., 15(3), 253(1999)

59) T. Nishide, Journal of Materials Science., 35, 465(2000)

60) H.D. Revana Siddapa, B. Vijaya, L. Shiva Kiimar and K. Shiva Pmsad, world Journal of Chemistry, 5(1), 18(2010)

62) N.Bharti, R.M. Maurya, F.Naqvi, A Bhattacharya, S. Bhattacharya, A. Azam, Eur. J.Med. Chem. 35, 481, (2000)

63) U. Kohn, M. Schulz, M. Gorls, E.A nders, Tetrahedron; Asymmetry 16, 2125, (2005).

64) R.G.S. Berlinck, M.H. Kossuga, A.M. Nascimento, Sci. Synth. 18, 1077, (2005)

65) T. Gupta, A.K. Patra, S. Dhar, M. Nethaji and A. R. Chakravarthy, J. Chem Sci. 117, 123, (2005)

66) E. Malhotra, N.K. Kaushik, H.S. Malhotra, Iridian J. of Chem. Sec (A), 45A. 370 (2006)

67) A.N.M. Kasim, D. Venkappayya, GV. Prabhu, J. Iridian Chem. Soc. 76, 67, (1999)

68) N. Raman, A. Kulandaisamy, C. Thangaraja, Transition Met. Chem. 29, 129, (2004)

69) F.A. Kettle, Coordination Compounds, (Thomas Nelson & Sons) 1975

70) A. Gingras, R.L. Somarjai, GS. Bayley, Can. J. Chem., 30, 1865, (1968)

71) B.T. Thaker, P.K. Tandel, A.S. Patel, C.J.Vyas, M.S. Jesani, D.M. Patel, Indian J. Chem. Sec(A) 44A, 265, (2005)

72) B.J. Hathaway, A. A.G Tomlinson, Coord. Chem. Rev. 5, 1, (1970)

73) R. Seangprasertkij, T.L. Riechel, Inorg, Chem. 23, 991, (1984)

74) R. Srinivasan, I. Sougandi, R. Venkatesan, P. Sambasivarao, Proc. Indian Acad. Sci. (Chem Sci) 115,91, (2003)

75) K. Hussain Reddy, P. Sambasiva Reddy, P. Ravindra Babu, J. Biochem., 11, 169, (1999)

76) B. Macias, I. Garcia, M.V. Villa, J. Borras, M.G. Alvarez, A. Castineiras, J. Inorg. BioChem. 96, 367, (2003)

77) P. Marfey, E. Robinson, Mutat, Res. 86, 1585, (1981)

78) J.C. Vincent, H.W. Vincent, Pros. Soc. Exptl. Biol. Medi., 55, 162, (1944)

79) R. S. Srivastava, Inorg, Chim. Acta. 56,65, (1944)

80) N. Gupta, R. Swaroop, R.V. Singh, Main Group Met. Chem. 114, 387, (1997)

81) L. Mishra, P.K. Singh, Iridian G. of Chem. Sec(A) 32A, 446, (1997)

82) R.Malhotra, S. Kumar, K.S. Dhindsa, Indian J. Chem. Sec(A) 32A, 457, (1993)

83) W. Levinson, E. Jawetz, Medical microbiology and immunology, (4^{th} Ed., Stamford), 1996

84) R.M. Roat. Bioinorganic Chemistry: A Short Course, Wyley Interseience, Hoboken, NJ (2002)

85) J.P. Kokko, J.H. Goldstein, L. Mandell. J. A m. Chem. Soc., 83, 2909 (1961).

86) J.W. Steed. J.L. Atwood Supramolecular Chemistry, Seconded., Wiley, New York, 2000.

87) J.P. Sauvage, Transition Metals in Supramolecular Chemistry, 5, Wiley, New York, 1999

88) B.N. Sivasankar, S. Govindarajan, Studies on bis(Hydrazine) metal malonates and succinates, J. Synth, React, Inorg, Metorg. Chem. 24 (1994) 1572-1582

89) L. Vikram, B.N. Sivasankar, Hydrazinium metal (II) and metal Calorim, 91 (2008) 963-970

90) J.X. Chen, S.X. Liu, E.Q. Gao, Syntheses, Structures and fluorescence of three novel 3D coordination polymers, J. Polyhedron 23 (2004) 1877-1888

91) A.I Vogel, Volumetric (titrimetric) analysis, in: A Text Book of Quantitative Inorganic Analysis, third ed., Longman, London, 1975, p. 380

92) A.B.P. Lever, Inorganic Electronic Spectroscopy, second ed. Elsevier: Amsterdam. 1894

93) A.B.P. Lever, Electronic spectra of some transition metal complexes: Derivation of Dq and B. J. Chem. Educ. 45 (11) (1968) 711

94) K.Nakamoto, Infrared and Raman Spectra of Inorganic and Coordination Compounds, Wiley, New York, 1978

95) D. Kivelson, R. Neiman. ESR Studies on the bonding of copper complexes, J. Chem. Phys. 35 (1961) 149

96) B.N. Sivasankar, S. Govindarajan, Hydrazine mixed metal malonates- New precursors for metal cobaltites, J. Mater, Res Bull, 31 (1966) 47-54

97) K. Saravnan, S. Govindarajan Dipicolonate complexes of main group metals with hydrazinium cation, J. Chem. Sci. 114 (2002) 25-36

98) P.R. Murray. E.J. Raron, M.A. Pfaller, F.C. Tenover, R.H. Yolke, Manual of Clinical Microbiology, ASM, Washington. DC, 1995. p 6

99) Merchant, B. Gold, the noble metal and the paradoxes of its toxicology. Biologicals 1998, 26, 49-59

100) Rosenberg, B. Platinum complexes for the treatment of cancer. Interdiscipl. Sci. Rev. 1978, 3, 134-147

101) Sadler, P.J. The biological chemistry of gold. Struct. Bond 1984, 29, 171-214

102) Cowan, J.A. Inorganic Biochemstry, 2nd ed.; Wiley-VCH: New York, NY, USA, 1997

103) Clark, M.J.E. Ruthenium and Other Metal Complexes in Cancer Chemotherapy; Springer -Verlag: Heidelberg, Cermany, 1989

104) Kobayashi, M.; Shimizu, S. Cobalt proteins. Eur. J. Biochem. 1999, 261, 1-9

105) Schwartz, J.A.; Lium, E.K.; Silverstein, S.J. Herpes simplex virus type 1 entry is inhibited by the cobalt chelate complex CTC-96. J. Virol. 2001, 75, 4117-4128

106) Redox Pharmaceutical Cooperation Home Page. http://www.redoxpharm.com/, (accessed on 25 May 2010)

107) Louie, A.Y.; Meade, T.J. A cobalt complex that selectively disrupts the structure and function of zinc fingers. Proc. Natl. Acad. Sci. USA 1998, 95, 6663-6668

108) Wooley, P.H.; Whalen, J.D. The influence of superoxide scavenging compound CTC-23 on type II collagen-induced arthritis in mice. Agents Actions 1992, 35, 273-279

109) Delehanty, J.B.; Bongard, J.E.; Thach, D.C.; Knight, D.A.; Hickey, T.E.; chang, E.L. Antiviral properties of cobalt(III)-complexes. Bioorg. Med. Chem. 2008, 16, 830-837

110) Canpolat, E.; Kaya, M. Synthesis, characterization of some Co(III) complexes with vic-ioxime ligands and their antimicrobial properties. Turk. J. Chem. 2004, 28, 235-242

111) Murukan, B.; Mohanan, K. Studies on some trivalent transition metal complexes with a bishydrazone. J. Saudi Chem. Soc. 2006, 10, 261-270

112) Navaneetha, N.; Nagarjun, P.A.; Satyanarayana, S. Study of the spectroscopic characteristics of methyl (ligand) cobaloximes and their antibacterial activity. J. Chem. Sci. 2007, 119, 29-34

113) Barceloux, D.G.; Barceloux, D. Cobalt, Clin. Toxicol. 1999, 37, 201-206

114) Naura, A.S.' Sharma, R. Toxic effects of hexaammine cobalt(III) chloride on liver and kidney in mice: Implication of oxidative stress, Drug Chem. Toxicol. 2009, 32, 293-299

115) Kalns, J. Brooks AFB, Texas, USA. Personal communication.

Signature Signature

Research Scholar

Research Supervisor

Dr. S.D. Dhage

M.Sc. M. Phil. Ph D.

(Research Guide in Chemistry)